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Association of Time of Day When Endovascular Therapy for Stroke Starts and Functional Outcome

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Objective: To investigate the association between EVT start time in acute ischemic stroke (AIS) and mid-term functional outcome.

Methods: This retrospective cohort study included all AIS cases treated with EVT from two stroke center registries from January 2012 to December 2018. The primary outcome was the score on the modified Rankin Scale (mRS) and the utility-weighted mRS (uw-mRS) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention at a given EVT start time would lead to lower scores on the mRS (shift analysis).

Results: One thousand five hundred fifty-eight cases were equally allotted into twelve EVT-start-time periods. The primary outcome favored EVT start times in the morning at 08:00-10:20 and 10:20-11:34 (common odds ratio (OR), 0.53; 95% confidence interval (CI), 0.38 to 0.75; $P<0.001$; OR, 0.62; 95% CI, 0.44 to 0.87; $P=0.006$, respectively), while it disfavored EVT start times at the end of the working day at 15:55-17:15 and 18:55-20:55 (OR, 1.47; 95% CI, 1.03 to 2.09; $P=0.034$; OR, 1.49; 95% CI, 1.03 to 2.15; $P=0.033$). Symptom onset-to-EVT start time was significantly higher and use of IV t-PA significantly lower between 10:20-11:34 ($P<0.004$ and $P=0.012$, respectively).

Conclusion: EVT for AIS in the morning leads to better mid-term functional outcome, while EVT at the end of the work day leads to poorer mid-term functional outcome. Neither difference in baseline factors, standard workflow and technical efficacy metrics could be identified as potential mediators of this effect.

Introduction

Research on occupational accidents indicates that the risk of accidents while working increases as a function of number of hours at work.¹⁻³ Hänecke and colleagues reported an exponential increase in occupational accidents after the ninth hour of work.⁴ Although most countries officially define the workday as eight hours, many doctors experience working hours well-beyond nine hours due to the need of 24-hour patient-care coverage.^{5, 6} Neurointerventionists and the rest of the stroke management team are currently feeling the effects of the changes in acute ischemic stroke (AIS) management,⁷ due in part to the mounting level of evidence from several large randomized controlled studies since 2015 that demonstrated the value of endovascular therapy (EVT) for first-line and delayed treatment.⁸⁻¹⁷ The significant increase in the number of EVT-eligible patients has proportionally increased the emergency case-load for the neurointerventionists as well as the whole support staff in the stroke unit which extends the number of hours at work and could be a potential source of fatigue.¹⁸ The need to examine the effects of doctor fatigue on the mid-term outcome of treated patients was recognized and reported in the literature.¹⁹ Current data on mid-term functional outcome in patients treated during work hours versus after hours is limited requiring more robust studies to elucidate the effects on patients treated at different times of the day.²⁰ We sought to investigate the association between EVT performed by presumed fatigued neurointerventionists and the stroke unit staff after standard working hours and the mid-term neurological outcome in treated patients.

Methods

Patient population:

We used two institutional databases, the acute stroke registry and analysis of Lausanne (ASTRAL) from Lausanne University hospital, Switzerland and the stroke registry from University Hospital of Bern, Bern, Switzerland; to retrospectively include all adult AIS patients who received EVT, either as thromboaspiration and/or mechanical thrombectomy according to institutional guidelines, from January 2012 to December 2018. For patient selection, we used the following inclusion criteria: AIS secondary to a large vessel intracranial occlusion, CT-based multimodal imaging performed within 24 hours of last proof of good health showing occlusion of an intracranial vessel amenable to EVT, brain angiography of good quality showing results following recanalization. Extracranial internal carotid artery occlusion or symptomatic stenosis without intracranial occlusion were excluded.

Both hospitals feature a comprehensive stroke center accredited by the Swiss Federation of Clinical Neurosocieties Swiss Stroke Committee mainly based on recommendations of the Swiss Stroke Society and European Stroke Organisation. Stroke team composition was similar among both centers and included an onsite neurologist trainee, on-call stroke attending neurologist, onsite attending anesthesiologist, and on-call attending interventional neurologist at all times including standard working hours, nighttime, and weekends. Imaging protocol and EVT criteria were based on local institutional guidelines and were applied in the same way regardless of admission day or time. For the University Hospital of Bern, MRI is performed during night and daytime and there are no differences in its availability. Indications for EVT are standardized according to an institutional operating procedure scheme. For Lausanne University Hospital, a dedicated emergency MR imager is available 24 hours a day, 7 days a week. It prioritizes stroke cases and there are no differences in its availability during nighttime and weekends relative to daytime.

Indications for EVT are identical to those mentioned in the operating procedures of University Hospital of Bern. Transfer patients were generally not re-imaged unless transfer times were greater than 1.5 hours or the patient severely deteriorated after thrombolysis. In these two situations, perfusion-CT/MRI was repeated prior to EVT. Both centers have between four and six interventional neuroradiologists in order to provide one on-call physician per center working in 24-hour shifts covering five to seven days per month. Approximately five EVTs are performed at Lausanne University and seven at University Hospital of Bern per week. During EVT, operators work almost exclusively independently with one angiography-suite technician working in eight-hour shifts providing technical and material support. Endovascular trainees are oftentimes present during EVT, but do not participate as primary or secondary operators. Finally, a wide array of stent retriever devices are used in these centers to perform EVT including, but not limited to Trevo (Stryker, Kalamazoo, Michigan, USA), Solitaire (Medtronic, Irvine, California, USA), Embotrap (Cerenovus, Galway, Ireland), Catch (Balt Extrusion, Montmorency, France) and Tiger (Rapid Medical, Yokneam, Israel).

Data collection:

Stroke-time onset and/or last time seen without symptoms, groin puncture-time and recanalization time were recorded for each patient. The EVT start time was considered the operator's groin-puncture-time. A disproportionate number of EVTs were performed during normal working hours, making analysis at fixed time intervals with unequal cohort sizes a potential source of bias. As a result, patients were divided into twelve cohorts containing the same number of patients according to EVT start time, beginning at 08:00, the start of the work day, until 07:59 the following day. Time periods varied between cohorts, with those during the day shorter and those at night longer. To perform a multivariate analysis and eliminate confounding factors,

the following patient characteristics were recorded: age, sex, atrial fibrillation, smoking, diabetes, hypertension, and hyperlipidemia, as well as stroke characteristics including, National Institutes of Health Stroke Scale (NIHSS) score at admission, pre-stroke modified Rankin Scale score (mRS), Alberta stroke program early CT score (ASPECTS), occlusion site, pre-stroke utility-weighted modified Rankin Scale score (uw-mRS), concomitant iv t-PA (tissue plasminogen activator), Trial of ORG 10172 in Acute Stroke Treatment (TOAST) mechanism type, symptom onset-to-EVT start time, admission-to-EVT start time and occlusion site; defined as: 1-Large-artery atherosclerosis, 2-Cardioembolism, 3-Small-vessel occlusion, 4-Stroke of other determined aetiology, and 5-Stroke of undetermined etiology.²¹ The EVT characteristics reported included the following: modified treatment in cerebral ischemia (mTICI) score, number of EVT passes, symptomatic intracranial haemorrhage (sICH), and uw-mRS at 90 days post-EVT.^{22, 23}

Primary and secondary outcomes:

The primary outcome of the study was the score on the modified Rankin scale at 90 days after EVT, which was assessed by trained personnel who were unaware of the EVT start time. The modified Rankin scale is a graded interval scale (range, 0 [no symptoms] to 6 [death]) for the assessment of neurologic functional disability.

Secondary outcomes included EVT start-to-recanalization interval time, mTICI score, number of EVT passes, and rate of sICH.

Statistical analyses:

Our analyses were performed to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between each EVT time start time, with scores of 5 (bedbound with severe disability) and 6 (death) combined due to comparable patient-centered outcome and with the assumption that the differential effect would lead to a

common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 0.6 for positive effects and 1.4 for negative effects.²⁴

Comparisons of baseline characteristics between cohorts were conducted using a one-way ANOVA for continuous variables of interest (age, NIHSS at admission, onset-to-EVT start time, number of EVT passes, baseline, EVT start-to-recanalization time, and uw-mRS at 90 days). Chi-square analysis was conducted for categorical variables of interest (atrial fibrillation, hypertension, smoking, diabetes, hyperlipidaemia, intravenous t-PA, TOAST, baseline, mTICI, and sICH). Continuous variables were presented using mean and interquartile range (IQR). Categorical variables were presented as frequencies with percentages. Significance was set at $p < 0.05$.

Detection of statistically significant variables was performed by a univariate analysis using an unpaired t-test comparing one cohort to all other reference cohorts, then subsequently repeated for other cohorts. Significance was set at $p < 0.05$.

Adjusted estimates of effect were selected according to clinical relevance and adjusted for age, symptom onset-to-EVT start time, age, NIHSS score, mTICI score, hypertension, and pre-stroke modified Rankin Scale score. The assessment of heterogeneity of EVT start time effect was performed with the inclusion of multiplicative interaction terms. Significance was set at $p < 0.05$.

Statistical analyses were performed using Anaconda version 5.3.1 (Anaconda, Austin, Texas, United States) for Python 2.7 (PSF, Delaware, United States) linked via module Rpy2 with R version 3.5.1ci (R Foundation, Vienna, Austria). For the primary endpoint, an ordinal multivariate logistic regression was performed with proportional odds ratio. To perform it, a Vector Generalized Linear and Additive Models (VGLM/VGAM) library was used in R. The confounding factors added into the

model were selected by clinical relevance. Non-collinearity was verified using tolerance metric in the R package 'olsrr.' All variables had a tolerance greater than 0.2 with the lowest tolerance calculated at 0.23. This confirmed our clinical assumption of no collinearity between variables.

Standard Protocol Approvals, Registrations, and Patient Consents:

The study was approved by the local institutional review board of each hospital under the auspices of the Swiss ethics committees for research involving humans (Swissethics). No informed consent was required according to the legislation.

Data Availability:

Individual deidentified participant data, related documents such as study protocol, and statistical analysis will be shared on request from any qualified investigator for three years after the date of publication.

Results

A total of 1,574 EVT consecutive procedures meeting selection criteria were selected for review, with 991 cases derived from University Hospital of Bern of which 660 were direct presentations (66%) and 581 from Lausanne University Hospital of which 490 were direct presentations (83%). Sixteen cases were lost on follow-up as no information on mid-term functional neurological status was available. The 1,558 cases available for analysis were distributed according to EVT start time into equal size patient-cohort time periods, each containing 127 to 131 patients. The cohorts were as follows: 08:00-10:20, 10:20-11:34, 11:34-12:40, 12:40-13:37, 13:37-14:41, 14:41-15:55, 15:55-17:15, 17:15-18:55, 18:55-20:55, 20:55-22:57, 22:57-02:07 and 02:07-07:58

Demographics, cardiovascular risk factors, and stroke characteristics:

A description of the demographics and cardiovascular risk factors for each patient cohort is shown in table 1. In summary, no inhomogeneity was detected in patient cohorts relating to demographics and cardiovascular risk factors with the exception of age; a small, yet statistically significant younger population was observed in the morning 08:00-10:20 cohort ($P=0.002$). The absolute difference of mean age between patients in this cohort relative to the mean of all patients included in the study was 3.5 years. Additionally, fewer patients in this cohort were hypertensive ($P=0.025$). A description of stroke characteristics for each patient cohort is shown in table 2. Stroke characteristics were similarly homogenous with the exception of symptom onset-to-EVT start time, IV t-PA use and admission-to-EVT start time. Onset-to-EVT start time was significantly longer between 10:20-11:34 and 02:07-07:58, while significantly shorter between 20:55-22:57 and 22:57-02:07 ($P=0.004$). Intravenous t-PA was used less frequently between 10:20-11:34 and 02:07-07:58 ($P=0.012$). Admission-to-EVT start time was significantly longer between 02:07-07:58. A description of stroke occlusion site is shown in table 3. Distribution of stroke occlusion site was homogenous among all cohorts.

Primary endpoint, EVT-start time and mid-term functional outcome:

Table 4 describes the univariate and multivariate analyses investigating the relationship between the EVT-start time and mRS, uw-mRS and mortality at 90 days. Analysis of the primary end point showed a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 0.53 (95% confidence interval [CI], 0.38 to 0.75, $P<0.001$) and of 0.62 (95% CI, 0.44 to 0.87, $P=0.006$) favoring EVT with start times in the morning at 08:00-10:20 and 10:20-11:34 as well as 1.47 (95% CI, 1.03 to 2.09, $P=0.034$) and 1.49 (95% CI, 1.03 to 2.15, $P=0.033$) at 15:55-17:15 and 18:55-20:55, respectively, disfavoring EVT at start times at the end

of the work day. Figure 1 shows the effect size in the primary end point across all EVT start time cohorts. There was a higher uw-mRS at 90 days signifying better functional outcome in patients with EVT performed between 08:00-10:20 (5.9, 95% CI, 3.3 to 9.1, $p<0.001$) as well as EVT performed between 10:20-11:34 (5.2, 95% CI, 0.0 to 9.1, $p=0.008$) and significantly lower uw-mRS signifying poorer functional outcome in patients treated at 15:55-17:15 (5.0, 95% CI, 0.0 to 8.4, $p=0.017$) ($P=0.017$). Figure 2 depicts the uw-mRS at 90 days as a function of time-period cohort for both stroke centres. Similar trends in functional outcome are observed in each stroke centre.

The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 37.6% and 37.2% when EVT start times were between 08:00-10:20 and 10:20-11:34, respectively, while only 22.5% and 19.0% for EVT start times at 15:55 and 18:55-20:55. Mortality at 90 days was lower in the morning in 12.8 % patients with EVT start time at 08:00-10:20 (OR: 0.52; 95% CI, 0.28 - 0.90); $P = 0.028$) and higher in at the end of the workday in 32.5% patients when EVT start times were 15:55-17:15 (OR: 1.78; 95% CI, 1.21 - 2.79); $P = 0.013$)

Secondary endpoints, EVT procedural characteristics:

Table 5 describes the univariate analysis of EVT characteristics in all time-period cohorts. In summary, mTICI score, number of EVT passes, presence of sICH and EVT start-to-recanalization time were not significantly different.

Discussion

The main finding of the present study is that mid-term functional outcome and mortality after EVT in AIS varied according to the start time of thrombectomy. EVT performed in the morning, 08:00-10:15, yielded good functional outcomes, whereas EVT performed after the ninth hour of work, 15:55-17:15, lead to poorer functional

outcomes. Surprisingly, outcome from EVT performed at nighttime is not significantly worse than EVT performed during the day. The difference observed does not seem to be caused neither by differences in baseline characteristics nor due to difference in standard measures of interventional efficacy and safety at different time points.

Endovascular therapy is a procedure requiring a high degree of vigilance and reflex, developed after several years of specialized training that may become impaired due to extended working hours.²⁵ Patients admitted out of normal work hours are less likely to be managed according to current operational guidelines leading to poorer short-term outcomes than those admitted during normal work hours.²⁶ We hypothesized that EVT performed outside of the workday or at night would lead to poorer mid-term functional outcome because of doctor fatigue. The link between fatigue and performance remains controversial, with some studies failing to demonstrate any correlation between extended working hours worked and doctor performance or safety outcomes.²⁷ A systematic literature review by Gates and colleagues suggests that evidence for possible association of doctor fatigue with performance is varied in part because of the use of heterogeneous outcome measurements.¹⁹ In stroke management, the outcomes of interest are mid-term functionality graded on the mRS and uw-mRS, a patient-centred scale that measures benefit of a given intervention to the patient.²³ We studied effect on mRS as a function of EVT-start time. Assuming that the on-call neurointerventionist begins his workday between 07:00 and 08:00, our study suggests that at the start of the workday, between 08:00-10:31, technical performance is optimal in a rested and vigilant doctor leading to the significantly higher uw-mRS at 90 days, or better mid-term functional outcome observed. However, the analyses of the secondary endpoints measuring technical performance did not reveal higher rates of complete recanalization, fewer numbers of EVT passes,

faster procedure times or lower rates of sICH. Notably, in this cohort, symptom onset-to-EVT start times were significantly longer and on average beyond 4.5 hours. This may suggest that many patients in this cohort met the stricter EVT requirements and thus had relatively better collateral circulation and smaller core infarct sizes, which could be a potential source of selection bias. Any possible inhomogeneity between cohorts cannot be corroborated because these two stroke characteristics were not recorded in the majority of patients in the two institutional databases used in this study. We hypothesize that in the morning cohorts, an increased number of stroke patients of unknown onset with limited infarct core size due to good collateralization were selected for EVT and thus had a higher probability of favorable mid-term functional outcome. These patients were statistically younger than other cohorts thus had better leptomeningeal collateral circulation and better hemodynamic variables with hypothetically small core size volumes. This cannot be substantiated in this study because infarct volume size was not available for analysis in this dataset.^{28,29} Also, only 66.4% patients at 08:00-10:15 were hypertensive compared to a frequency of 74.7% for all groups. While concomitant hypertension in AIS is associated with poorer outcome and therefore could in part explain better outcome in the morning cohorts, we do not observe a statistically poorer outcome in cohorts with higher frequency hypertension. Additionally, any inhomogeneity in rates of hypertension among the cohorts cannot solely explain, according to the applied statistical model, the difference in mid-term functional outcome.³⁰ Moreover, this could also indicate that a large number of patients were deemed unsuitable, but possibly could of benefitted from EVT.

Conversely, EVTs performed between 15:55-17:15, after a nine-hour workday, were associated with higher mRS at 90 days or poorer mid-term functional functional outcome. Although, our multivariate analysis showed significantly higher mRS at 90 days, intermediate outcome measurements that have predictive effects on mid-term

functional outcome, like mTICI, number of EVT passes, rate of sICH were not significantly altered in this time period.³¹⁻³³ Moreover, EVT start-to-recanalization time, a measure of technical skill, and rapidity, was not significantly different between time-period cohorts. We therefore hypothesize that other factors independent of doctor fatigue, such as stroke team shift changes or hampered performance from other collaborators such as emergency neurologist or support staff in the stroke unit, may contribute to poor functional outcome. Figure 3 shows the work shifts for interventional neuroradiology, stroke unit and emergency neurology physicians at both centers.

Additionally, the observed outcome decline between 15:55-17:15 was only transient, with values of uw-mRS at 90 days actually increasing after 17:15, at the end of the standard work day in our two hospitals. Admission-to-groin puncture delay were significantly longer at night, which has been previously reported.^{34, 35} Corroborating the findings of the MR CLEAn Registry, this delay was not appreciable in our analysis regarding clinical outcome. We conjecture that working conditions for EVT paradoxically improves during the evening or night and may maintain good technical performance and offset fatigue partially because of less work burden and/or distractions. Studies on work-related injuries as a function of the number of hours worked, showed a transient, yet significant increase after the ninth hour of work, but a non significant risk thereafter or at nighttime.^{4, 36} The results of this study show similar findings regarding functional outcome and highlights similar trends in both stroke centres included in this study.

Finally, the repercussions of the burgeoning demand for EVT due to recent paradigm shifts of AIS management on neurointerventionists and the stroke unit staff remains controversial.²⁵ Previously, AIS stroke management was limited to IVT, requiring knowledge but not depending on technical skill. Nowadays, the complexities involved in EVT during AIS management, poses challenges to neurointerventionists,

anaesthetists, and stroke unit staff faced with increasing caseload, extended working hours, and more on-call duties. Our data show differences in outcome warranting further investigation of current workplace conditions for EVT in AIS on patient outcome.

Limitations:

One of the weaknesses of this study is that many of the confounding variables cannot be controlled in the analyses, such as variability in a doctor's skill, training level or overall stroke-unit performance. For example, interruptions of activity related to shift changes, patient transferring, and diagnostic exams during the day may decrease the amount of time for direct patient care in certain cohorts leading to adverse effects prior to or following EVT. Any potential difference may also be observed between the hospitals included in this study as Lausanne University Hospital performs fewer EVTs than University Hospital of Bern. Nevertheless, the subgroup analysis of uw-mRS at 90 days for each hospital reveals similar trends as a function of EVT-start time, most notably at 15:54-17:15. Moreover, the addition of center variables, such as hospital site or weekday versus weekend, to the logistic regression did not affect results. Additionally, perfusion imaging data and infarct core size score were not available for analysis and inhomogeneity in these characteristics among the cohorts may explain differences in clinical outcome. Other limitations include the fact that this study is retrospective and includes AIS patients treated by EVT from 2012, an era when EVT was less standardized.

Conclusion

EVT for AIS patients performed in the morning between 08:00-10:20 leads to better mid-term functional outcome at 90 days, despite having a statistically longer symptom onset-to-EVT start time delay, while EVT performed at the end of the

working day, between 15:54-17:15, leads to poorer neurological outcome. Additional prospective studies data are required to support our findings and further analysis regarding causal relation are warranted.

Appendix 1: Authors

Name	Location	Contribution
Steven D Hajdu	Lausanne University Hospital, Lausanne, Switzerland	Design and conceptualized study; data analysis; drafted and revised the manuscript for intellectual content
Johannes Kaesmacher	University Hospital of Bern, Bern, Switzerland	Design and conceptualized study; data analysis; drafted and revised the manuscript for intellectual

		content
Patrik Michel	Lausanne University Hospital, Lausanne, Switzerland	Major role in acquisition of data; interpreted the data
Gaia Sirimarco	Lausanne University Hospital, Lausanne, Switzerland	Interpreted the data; revised the manuscript for intellectual content
Jean-Francois Knebel	Lausanne University Hospital, Lausanne, Switzerland	Performed statistical analysis
Bruno Bartolini	Lausanne University Hospital, Lausanne, Switzerland	Major role in acquisition of data
Christoph C Kurmann	University Hospital of Bern, Bern, Switzerland	Major role in acquisition of data
Francesco Puccinelli	Lausanne University Hospital, Lausanne, Switzerland	Major role in acquisition of data
Pascal J Mosimann	University Hospital of Bern, Bern, Switzerland	Major role in acquisition of data
Christophe Bonvin	Sion Hospital, Sion, Switzerland	Major role in acquisition of data
Marcel Arnold	University Hospital of Bern, Bern, Switzerland	Major role in acquisition of data
Julien Niederhäuser	Nyon Regional Hospital, Nyon, Switzerland	Major role in acquisition of data
Ashraf Eskandari	Lausanne University Hospital, Lausanne, Switzerland	Interpreted the data
Pasquale Mordasini	University Hospital of Bern, Bern, Switzerland	Major role in acquisition of data
Jan Gralla	University Hospital of Bern, Bern, Switzerland	Major role in acquisition of data; study design
Urs Fischer	University Hospital of Bern, Bern, Switzerland	Design and conceptualized study; data analysis; drafted the manuscript for intellectual content
Guillaume Saliou	Lausanne University Hospital, Lausanne, Switzerland	Design and conceptualized study; data analysis; drafted the manuscript for intellectual content

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Figure 1. Analysis of the Primary Endpoint.

The forest plot shows the effect size in the primary endpoint (common odds ratio for improvement on the modified Rankin scale at 90 days, analyzed according to ordinal logistic regression and adjusted for age, symptom onset-to-EVT start time, age, National Institutes of Health Stroke Scale score, modified treatment in cerebral ischemia score, and pre-stroke modified Rankin Scale score) across all EVT start time cohorts.

There are significant differences in the morning cohorts at 08:00-10:20 and 10:20-11:34 suggesting better functional outcome at three months as well as in the end-of-workday cohorts at 15:55-17:15 and 18:55-20:55 suggesting poorer functional outcome at three months.

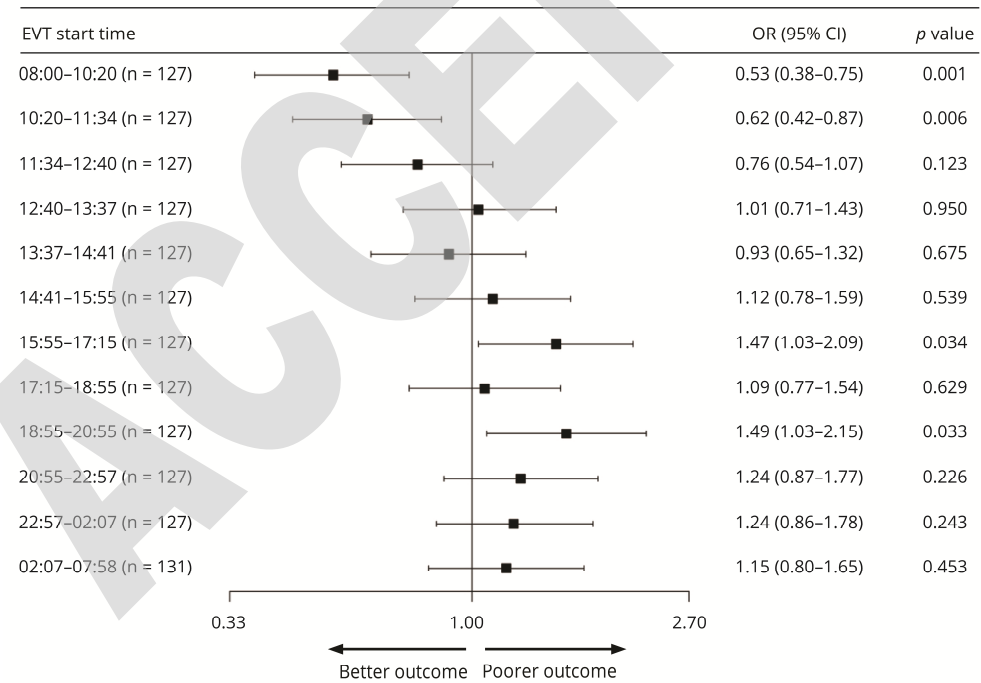


Figure 2. Scores on the utility-weighted modified Rankin Scale at 90 days for each stroke center as a function of endovascular therapy start time.

Data are organized into twelve equally-sized cohorts over 24 hours starting at 8:00.

Higher scores indicated better functional outcome. Green shading corresponds to cohorts with favorable functional outcome at three months, while red shading corresponds to cohorts with poorer functional outcome at three months.

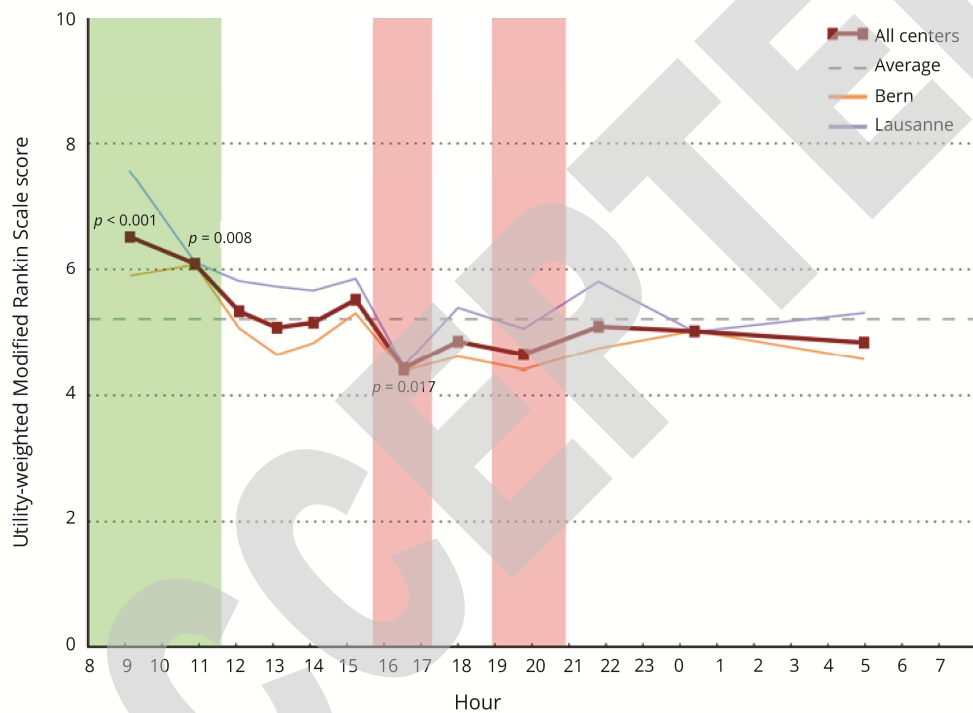


Figure 3. Shift schedules for physicians in interventional neuroradiology (INR), stroke unit (SU) and emergency neurology (EN).

Data are organized into twelve equally sized cohorts over 24 hours starting at 8:00.

Green shading corresponds to cohorts with favorable functional outcome at three months, while red shading corresponds to cohorts with poorer functional outcome at three months.



Table 1: Patient characteristics and cardiovascular risk factors

	Total	08:00-10:20 (n=127)	10:20-11:34 (n=127)	11:34-12:40 (n=127)	12:40-13:37 (n=127)	13:37-14:41 (n=127)	14:41-15:55 (n=127)	15:55-17:15 (n=127)	17:15-18:55 (n=127)	18:55-20:55 (n=127)	20:55-22:57 (n=127)	22:57-02:07 (n=127)	02:07-07:58 (n=131)
Age, years	71.1 (62.4-82.0)	67.6 (57.7-78.7) ^a	70.8 (62.8-81.4)	73.6 (66.3-82.1)	71.1 (62.3-82.1)	75.0 (69.4-85.7)	72.7 (65.0-82.1)	70.9 (62.4-82.1)	70.4 (60.6-83.0)	70.2 (59.2-81.1)	69.9 (59.9-81.2)	72.2 (63.7-81.7)	68.9 (60.1-79.2)
Female sex	794/1527 (52.0)	72 (56.7)	75 (59.5)	62 (50.4)	62 (48.8)	58 (45.7)	57 (44.9)	60 (47.2)	69 (54.3)	68 (53.5)	61 (48.0)	70 (55.1)	78 (59.5)
Atrial fibrillation	630/1398 (45.1)	40 (33.6)	46 (39.0)	51 (43.6)	59 (49.6)	65 (54.2)	60 (52.2)	46 (40.7)	54 (46.6)	49 (43.4)	48 (43.2)	57 (49.1)	55 (45.5)
Smoking	413/1500 (27.5)	38 (30.2)	34 (27.0)	31 (24.6)	32 (25.6)	31 (24.8)	33 (27.5)	38 (30.9)	30 (24.0)	35 (27.8)	34 (27.4)	40 (31.8)	37 (28.9)
Diabetes	298/1506 (19.8)	22 (17.5)	30 (23.8)	21 (16.9)	16 (12.8)	23 (18.3)	26 (20.6)	28 (22.6)	26 (20.8)	30 (24.2)	30 (23.8)	23 (18.3)	23 (18.0)
Hyperlipidemia	1025/1515 (67.7)	86 (67.7)	82 (65.1)	95 (74.8)	82 (65.1)	92 (73.0)	83 (67.5)	84 (67.2)	85 (66.9)	84 (66.7)	72 (57.6)	86 (67.7)	94 (72.3)
Hypertension	1153/1542 (74.7)	85 (66.4) ^b	88 (67.7)	108 (82.4)	96 (73.3)	105 (82.7)	100 (78.7)	99 (76.7)	96 (73.9)	93 (72.7)	93 (73.2)	101 (79.5)	89 (69.5)

Data are mean (IQR) or n (%). ^a *P* value = 0.002, calculated using one-way ANOVA. ^b *P* value = 0.025, calculated using one-way ANOVA

Table 2: Stroke characteristics

	Total	08:00-10:20 (n=127)	10:20-11:34 (n=127)	11:34-12:40 (n=127)	12:40-13:37 (n=127)	13:37-14:41 (n=127)	14:41-15:55 (n=127)	15:55-17:15 (n=127)	17:15-18:55 (n=127)	18:55-20:55 (n=127)	20:55-22:57 (n=127)	22:57-02:07 (n=127)	02:07-07:58 (n=131)	P value
NIHSS at admission^a	14.8 (9.0-20.0)	14.4 (8.0-19.0)	13.1 (7.0-17.0)	16.0 (10.5-20.0)	14.7 (9.0-20.0)	15.5 (10.0-21.0)	13.4 (7.0-19.0)	15.0 (9.0-20.0)	14.7 (8.5-19.5)	15.0 (8.0-19.0)	15.1 (9.0-19.0)	14.8 (8.0-19.0)	16.3 (11.0-19.0)	0.051
ASPECTS^b	7.8 (7-10)	8 (7-9.5)	8 (7-9)	7.8 (6-10)	8.2 (7-10)	8 (7-9)	7.9 (7-10)	7.9 (6-10)	7.8 (7-9)	7.9 (7-10)	7.6 (7-9)	7.9 (7-9.5)	7.2 (6-9)	0.400
i.v. t-PA^c	792 (53.8)	60 (50.9)	49 (40.8)	62 (51.2)	73 (58.4)	67 (55.4)	71 (57.3)	76 (60.3)	75 (60.5)	68 (54.4)	59 (48.0)	75 (62.5)	57 (45.2)	0.012 ^h
TOAST^d														0.197
1	213 (14.2)	14 (11.1)	18 (14.4)	20 (15.8)	21 (16.8)	14 (11.5)	15 (12.0)	28 (22.4)	21 (16.5)	20 (16.0)	14 (11.3)	15 (11.9)	13 (10.2)	
2	638 (42.4)	48 (38.1)	45 (36.0)	52 (40.9)	61 (48.8)	64 (52.5)	61 (48.8)	50 (40.0)	48 (37.8)	47 (37.6)	54 (43.6)	55 (43.7)	53 (41.4)	
4	157 (10.4)	21 (16.7)	16 (12.8)	9 (7.1)	11 (8.8)	9 (7.4)	10 (8.0)	8 (6.4)	13 (10.2)	19 (15.2)	11 (8.9)	10 (7.9)	20 (15.6)	
5	488 (32.4)	42 (33.3)	45 (36.0)	46 (36.2)	31 (24.8)	35 (28.7)	39 (31.2)	38 (30.4)	44 (34.6)	38 (30.4)	45 (36.3)	45 (35.7)	40 (31.3)	
Prestroke mRS^e														0.833
0-2	1349 (89.5)	118 (94.4)	109 (87.9)	111 (87.4)	110 (88.0)	109 (88.6)	109 (88.6)	111 (89.5)	113 (89.7)	117 (92.9)	109 (87.9)	109 (88.6)	115 (89.8)	
3-5	158 (10.6)	7 (5.6)	15 (12.1)	16 (12.6)	15 (12.0)	14 (11.4)	14 (11.4)	13 (10.5)	13 (10.3)	9 (7.1)	15 (12.1)	14 (11.4)	14 (11.4)	
uw-mRS^f	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	9.9 (10.0-10.0)	0.833
Onset-to-EVT start time – (mins)^g	305 (178-350)	306 (152-435)	335 (169-422)	312 (178-330)	282 (170-274)	313 (192-323)	312 (164-347)	299 (166-357)	288 (166-334)	294 (184-324)	266 (169-304)	273 (200-314)	376 (245-462)	0.004 ⁱ
Admission-to-EVT start time – (mins)	102 (65-117)	97 (62-103)	96 (61-105)	87 (58-113)	85 (54-112)	95 (54-115)	98 (59-117)	110 (67-115)	110 (70-117)	106 (73-119)	93 (71-115)	110 (64-133)	133 (84-134)	0.001 ⁱ

Data are mean (IQR) or n (%). EVT=endovascular therapy. ^a Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42. Scores increase as a function of neurological deficit. ^b Alberta Stroke Program Early CT Score (ASPECTS) ranging from 0 to 10. ^c Intravenous treatment with tissue plasminogen activator (t-PA) was used up to 4.5 hours after symptom onset. 1473 patients analyzed. ^d Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification of subtypes of acute ischemic stroke are defined as: 1-Large-artery atherosclerosis, 2- Cardioembolism, 3- Small-vessel occlusion, 4-Stroke of other determined etiology and 5-Stroke of undetermined etiology. 1505 patients analyzed. ^e Scores on the modified Rankin scale: 0- no symptoms, 1- no clinically significant disability, 2- slight disability, 3- moderate disability, 4- moderately severe disability, 5- severe disability, 6- death. 1498 patients analyzed. ^f Score on utility-weighted modified Rankin scale (uw-mRS) ranges from 0: death to 10: no symptoms or disability. ^g EVT=endovascular therapy. ^h The P value was calculated using χ^2 -squared. ⁱ The P value was calculated using a one-way ANOVA.

Table 3: Occlusion site

	Total	08:00-10:20 (n=127)	10:20-11:34 (n=127)	11:34-12:40 (n=127)	12:40-13:37 (n=127)	13:37-14:41 (n=127)	14:41-15:55 (n=127)	15:55-17:15 (n=127)	17:15-18:55 (n=127)	18:55-20:55 (n=127)	20:55-22:57 (n=127)	22:57-02:07 (n=127)	02:07-07:58 (n=131)
Vertebral artery	18 (1.2)	1 (0.8)	0 (0)	2 (1.7)	1 (0.8)	1 (0.9)	0 (0)	5 (4.3)	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.7)	2 (1.7)
Basilar artery	21 (1.5)	2 (1.6)	1 (0.8)	1 (0.8)	3 (2.5)	2 (1.7)	0 (0)	2 (1.7)	1 (0.8)	3 (2.5)	2 (1.7)	3 (2.5)	1 (2.5)
Intracranial internal carotid artery ^a	319 (22.1)	23 (18.9)	26 (21.3)	25 (20.8)	29 (23.8)	29 (24.8)	21 (18.6)	19 (16.4)	26 (21.0)	34 (27.9)	30 (24.8)	23 (19.2)	34 (27.6)
First segment of middle cerebral artery	679 (47.1)	61 (50.0)	58 (47.5)	62 (51.7)	55 (45.1)	56 (47.9)	56 (49.6)	55 (47.4)	68 (54.8)	54 (44.3)	59 (48.8)	51 (42.5)	44 (35.8)
Second segment of middle cerebral artery	272 (18.9)	24 (19.7)	28 (23.0)	24 (20.0)	23 (18.9)	23 (19.7)	18 (15.9)	30 (25.9)	16 (12.9)	19 (15.6)	18 (14.9)	26 (21.7)	23 (18.7)
Third segment of middle cerebral artery	14 (1.0)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	0 (0)	2 (1.8)	0 (0)	2 (1.6)	2 (1.6)	2 (1.7)	1 (0.8)	1 (0.8)
Fourth segment of middle cerebral artery	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
First segment of anterior cerebral artery	4 (0.3)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	2 (1.6)	0 (0)	0 (0)	0 (0)
Second segment of anterior cerebral artery	4 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
First segment of posterior cerebral artery	104 (7.2)	10 (8.2)	6 (4.9)	5 (4.2)	10 (8.2)	4 (3.4)	14 (12.4)	5 (4.3)	7 (5.6)	7 (5.7)	9 (7.4)	11 (9.2)	16 (13.0)
Second segment of posterior cerebral artery	6 (0.4)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.9)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.7)	1 (0.8)

Data are n (%). 1442 patients analyzed. *P* value of 0.51 was calculated using χ -squared. ^a Patients who had occlusion of intracranial internal carotid artery (carotid terminus) may have also had thrombus extension into the first segment of either the anterior and/or the middle cerebral artery.

Table 4: Unadjusted and adjusted association between EVT start time and long-term neurological outcome

	Modified Rankin Scale score at 90 days ^a							Utility-weighted Modified Rankin Scale score at 90 days ^b	Reduction in Modified Rankin scale score at 90 days ^c		Mortality at 90 days
EVT start time	0	1	2	3	4	5	6		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^d	Adjusted Odds Ratio (95% CI)
08:00-10:20 (n=127)	15 (12.0)	32 (25.6)	35 (28.0)	13 (10.4)	9 (7.2)	5 (4.0)	16 (12.8)	6.6 (6.5-9.1) p<0.001	0.51 (0.37-0.70) p<0.001	0.53 (0.38-0.75) p<0.001	0.52 (0.28-0.90) p=0.028
10:20-11:34 (n=127)	20 (16.5)	25 (20.7)	20 (16.5)	13 (10.4)	16 (13.2)	7 (5.8)	19 (15.8)	6.0 (3.3-9.1) p=0.008	0.63 (0.46-0.88) p=0.006	0.62 (0.44-0.87) p=0.006	0.71 (0.40-1.20) p=0.223
11:34-12:40 (n=127)	14 (11.5)	18 (14.8)	18 (14.8)	23 (18.9)	13 (10.7)	6 (4.8)	30 (24.5)	5.2 (0.0-9.1) p=0.709	1.03 (0.74-1.43) p=0.853	0.76 (0.54-1.07) p=0.123	0.86 (0.52-1.37) p=0.534
12:40-13:37 (n=127)	10 (8.4)	21 (17.7)	21 (17.7)	16 (13.5)	19 (16.0)	6 (5.0)	26 (21.8)	5.2 (0.0-9.1) p=0.677	1.02 (0.73-1.42) p=0.919	1.01 (0.71-1.43) p=0.950	0.93 (0.55-1.51) p=0.773
13:37-14:41 (n=127)	13 (10.8)	19 (15.8)	17 (14.2)	23 (19.2)	9 (7.5)	10 (8.3)	29 (24.2)	5.1 (0.0-9.1) p=0.862	1.08 (0.77-1.50) p=0.656	0.93 (0.65-1.32) p=0.675	0.83 (0.50-1.35) p=0.471
14:41-15:55 (n=127)	12 (10.1)	19 (16.0)	26 (21.9)	23 (19.3)	8 (6.7)	5 (4.2)	26 (21.9)	5.6 (0.0-9.1) p=0.353	0.87 (0.62-1.21) p=0.407	1.12 (0.78-1.59) p=0.539	1.06 (0.63-1.73) p=0.825
15:55-17:15 (n=127)	11 (9.2)	16 (13.3)	20 (16.7)	10 (8.3)	16 (13.3)	8 (6.7)	39 (32.5)	4.4 (0.0-7.6) p=0.017	1.46 (1.05-2.05) p=0.025	1.47 (1.03-2.09) p=0.034	1.78 (1.21-2.79) p=0.013
17:15-18:55 (n=127)	12 (9.8)	19 (15.5)	23 (18.7)	17 (13.8)	12 (9.8)	8 (6.5)	32 (26.0)	5.0 (0.0-8.4) p=0.275	1.09 (0.79-1.52) p=0.596	1.09 (0.77-1.54) p=0.629	1.20 (0.74-1.91) p=0.447
18:55-20:55 (n=127)	9 (7.8)	13 (11.2)	23 (19.8)	12 (10.3)	18 (15.5)	9 (7.8)	32 (27.6)	4.5 (0.0-7.6) p=0.086	1.42 (1.01-1.99) p=0.042	1.49 (1.03-2.15) p=0.033	1.08 (0.65-1.73) p=0.773
20:55-22:57 (n=127)	11 (8.9)	22 (17.9)	17 (13.8)	19 (15.5)	20 (16.3)	6 (4.9)	28 (22.8)	5.1 (0.0-9.1) p=0.712	1.06 (0.76-1.47) p=0.736	1.24 (0.87-1.77) p=0.226	1.04 (0.62-1.68) p=0.879
22:57-02:07 (n=127)	10 (8.5)	19 (16.1)	23 (19.5)	14 (11.9)	14 (11.9)	6 (5.1)	32 (27.1)	4.9 (0.0-7.6) p=0.557	1.12 (0.80-1.57) p=0.495	1.24 (0.86-1.78) p=0.243	1.28 (0.78-2.05) p=0.312
02:07-07:58 (n=131)	8 (6.7)	15 (12.5)	24 (20.0)	19 (15.8)	16 (13.3)	8 (6.7)	30 (25.0)	4.8 (0.0-7.6) p=0.245	1.28 (0.92-1.78) p=0.152	1.15 (0.80-1.65) p=0.453	1.02 (0.61-1.64) p=0.947

Data are mean (IQR) or n (%). ^a Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Distribution of scores at 90 days for EVT start times in the overall trial population. ^b The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability). ^c The measurement of effect was a cumulative logistic-regression odds ratio (shift analysis). ^d Controlling for age, symptom onset-to-EVT start time, age, National Institutes of Health Stroke Scale score, modified treatment in cerebral ischemia score, and pre-stroke modified Rankin Scale score.

Table 5: Efficacy outcomes

	Total	08:00-10:20 (n=127)	10:20-11:34 (n=127)	11:34-12:40 (n=127)	12:40-13:37 (n=127)	13:37-14:41 (n=127)	14:41-15:55 (n=127)	15:55-17:15 (n=127)	17:15-18:55 (n=127)	18:55-20:55 (n=127)	20:55-22:57 (n=127)	22:57-02:07 (n=127)	02:07-07:58 (n=131)	P value
mTICI^a														0.0682
3	734/1526 (48.1)	51 (40.2)	62 (48.8)	66 (52.0)	62 (48.8)	61 (48.0)	60 (48.0)	62 (48.8)	55 (43.3)	58 (45.7)	72 (56.7)	55 (43.3)	70 (53.4)	
2b	528/1526 (34.6)	58 (45.7)	43 (33.9)	37 (29.1)	37 (29.1)	45 (35.4)	50 (40.0)	41 (32.3)	46 (36.2)	37 (29.1)	36 (28.4)	52 (40.9)	38 (29.0)	
0-2a	264/1526 (17.3)	18 (14.2)	22 (17.3)	24 (18.9)	20 (15.8)	21 (16.5)	15 (12.0)	24 (18.9)	26 (20.5)	32 (25.2)	19 (15.0)	20 (15.8)	23 (17.6)	
sICH^b	118/1476 (8.0)	5 (4.1)	10 (7.9)	9 (7.3)	8 (6.7)	10 (8.3)	9 (7.3)	13 (10.5)	7 (5.6)	9 (7.6)	10 (8.2)	10 (8.1)	18 (14.3)	0.374
EVT start-to-recanalization time (min)^c	58.0 (29-75)	56.1 (25-80)	59.9 (31-75)	65.9 (30-90)	60 (34-72)	57.7 (31-74)	55.4 (30-68)	58.9 (27-81)	52.0 (29-67)	52.0 (29-67)	50.4 (25-65)	59.7 (28-80)	57.8 (30-86)	0.282

Data are mean (IQR) or n (%). ^a Modified Thrombolysis in Cerebral Ischemia (mTICI) score: 2b or 3 indicates successful reperfusion. ^b Symptomatic intracranial hemorrhage (sICH). ^c EVT=endovascular therapy

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